Evidence-based Practice Center Systematic Review Protocol

Project Title: Identification and Treatment of Post-Acute Coronary Syndrome (ACS) Depression: A Systematic Review

I. Background and Objectives for the Systematic Review

Heart disease is the leading cause of death worldwide.[1] In the United States, where it is the leading cause of death for both men and women, heart disease accounts for more than 600,000 deaths annually, or 23.5% of deaths from all causes.[2] Over 25 million adults in the United States are currently estimated to be living with a diagnosis of heart disease,[3] and over 1 million people in the United States are estimated to be hospitalized for an acute coronary syndrome [i.e. unstable angina pectoris or myocardial infarction (MI)] each year.[4]

Patients who are diagnosed with acute coronary syndrome (ACS) are at risk for a range of negative health outcomes. For the purpose of this review, ACS refers to clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Post-ACS patients may be at greater risk for mental health problems—in particular, depression.[5] In the general population, lifetime prevalence of depression symptoms is approximately 17%,[6] studies however have found that as many as 65% of post-MI patients experience symptoms of depression.[7,8] Depressive disorders are characterized by persistent depressed mood or anhedonia, other associated symptoms such as sleep disturbance or decreased energy, and functional impairment for at least 2 weeks. Major depressive disorder (MDD), persistent depressive disorder (DSM-IV dysthymia), and subsyndromal depression are highly prevalent in general medical populations (2-16% within the US)[9-13] and are estimated as the second largest cause of loss in disability-adjusted life years.[14] Depressive disorders are associated with chronic medical illness, including cardiovascular disease, and worse general medical outcomes. Patients with depression post-MI have significantly increased risk of death.[15]

Despite the high prevalence of depression, the association with cardiovascular disease, and the profound impact on quality of life (QOL), there is considerable uncertainty about whether and how to screen patients for depression post-ACS.

Guidelines for screening for depression in primary care settings vary. The 2016 guidelines from the U.S. Preventive Services Task Force (USPSTF) recommend that depression screening be "implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow up."[16] However, other guidelines recommend targeted screening for patients at increased risk of depression[17]or against routine screening.[18] Individuals post-ACS are at higher risk for depression and some professional societies recommend routine screening during and after the post-MI hospitalization, but these guidelines are controversial.[19,20] It is unclear how well standard

Source: www.effectivehealthcare.ahrq.gov
Published online: August 29, 2016

instruments for detecting depression perform in this medically ill group and whether this group would benefit from targeted screening.

It is also unclear whether post-ACS patients with depression respond any differently than people in the general population with depression to commonly used, efficacious treatments for depression. Such treatments include pharmacotherapy and psychotherapy, with second generation antidepressants and cognitive behavioral therapy (CBT) being among the most widely supported, evidence-based, depression treatment approaches. Both pharmacotherapy and psychotherapy have been shown to be effective,[15] although it is unclear whether combination therapy is superior to pharmaco- or psychotherapy alone. It is possible, though not clearly established, that some of these treatments for depression may function differently in post-MI patients.[21] For instance, behavioral activation, a core component of many CBT-based approaches, might encourage the adoption of new behavioral repertoires that not only improve mood but also medical outcomes.[22] The same could be hypothesized about exercise, which has been demonstrated to have beneficial effects for emotional health[23] and cardiovascular health.[24] Alternatively, it may be that certain depression treatments that are usually effective in the general population are less so among post-ACS patients, or carry certain risks that might be of particular concern in this population.[21]

Depression treatments include antidepressant medications, adjunctive medications (e.g., atypical antipsychotics), psychotherapies, light therapy, supportive strategies (e.g., exercise, guided self-help), and combinations of these approaches. In addition, collaborative care, a method to improve care delivery, is a potential intervention of interest. For this review, we have expanded the scope to consider all patients with ACS (unstable angina and MI), criterion-based (DSM-V or equivalent) depressive disorders, and treatment approaches prioritized by the stakeholders and Technical Expert Panel. Given available resources and discussions with both the nominator and additional stakeholders, we will not include patients who are post-PCI or post-CABG. Discussion of the impact of this decision will be included in the report. Information on the FDA status and warnings for use the medications considered in this review are provided in Appendix A.

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from May 26, 2016 to June 15, 2016. Overall, the comments affirmed our planned approach. Specific suggestions included: (a) clarifying the screening tools to be considered and how International Classification of Diseases (ICD) diagnoses would be used in the context of a validated criterion standard, (b) adding transcranial magnetic stimulation, (c) clarifying aspects of the adverse effects to be considered, such as distinguishing between treatment discontinuation due to adverse effects vs efficacy and further distinguishing among suicide-related behaviors, and (d) clarifying other specific outcome elements. Revisions made in response include: clarifying the screening tools and adding the Quick Inventory of Depressive Symptomatology to the interventions of interest in KQ 1, clarifying handling of ICD diagnoses, adding transcranial magnetic stimulation as an intervention of interest for KQ 2, and clarifying adverse effects outcomes. Additional modifications to outcomes included explicitly adding remission

within the category of depression-related outcomes and specifying the types of emergency room visits of interest. There were no other significant changes to the KQs or proposed methods. Note that the scope of the review does not explicitly address the linkage between the use of screening tools in KQ1 and downstream clinical outcomes. This limitation in scope will be addressed in the discussion of the findings and highlighted as an area for potential future research. Also note that although ease of use and user burden are not listed within KQ1 as specific outcomes of interest, the systematic review will include a summary table of the screening tool characteristics (e.g., number of items, availability/fees) to aid in the comparison and intepretation of our findings.

KQ 1: What is the accuracy of depression screening instruments or screening strategies compared to a validated criterion standard for post-acute coronary syndrome (ACS)* patients?

- Population(s):
  - Adults who have acute coronary syndrome (ACS) [which includes both unstable angina and myocardial infarction (MI)] and are within 3 months of an identifying ACS event.
- Interventions:
  - Screening tools for depression,[25,26] limited to:
    - Beck Depression Inventory (multiple versions)
    - Center for Epidemiologic Studies-Depression (CES-D20 and CES-D10)
    - Distress Questionnaire 5 (DQ5)
    - Duke Anxiety and Depression Scale
    - Geriatric Depression Scale (GDS-15) [2 versions, long and short]
    - Hospital Anxiety and Depression Scale (HADS and HADS-D)
    - Diagnostic Inventory for Depression (DID)[27]
    - Kessler Psychological Distress Scale (K10 and K6)
    - Patient Health Questionnaire (PHQ-8/9 and 2)
    - Primary care rapid evaluation of mental disorders (PRIME-MD, including Whooley questions)
    - PROMIS® (Patient-Reported Outcomes Measurement Information System)
    - Quick Inventory of Depressive Symptomatology (QIDS)[28]
    - Symptom Checklist 20 and Hopkins Symptom Checklist
    - WHO-5 (World Health Organization-5)
    - Zung Self-Rating Depression Scale (SDS)
  - Screening strategies that differ by setting (i.e, inpatient vs outpatient, general medicine vs cardiology) or timing (i.e., duration post-ACS).
- Comparators:
  - Validated criterion standard (e.g., DSM or ICD criteria) administered by a trained interviewer
- Outcomes:
  - Diagnostic accuracy
    - Sensitivity

        - Specificity
        - Negative predictive value (NPV)
        - Positive predictive value (PPV)
        - Likelihood ratios
        - Receiver operating characteristic (ROC) curves
- Timing:
    - Within 3 months of an identifying ACS event
    - Intervals of interest:
        - During hospitalization/at discharge
        - Within 30 days of hospitalization for an acute ACS event
        - Within 3 months of hospitalization for an acute ACS event
- Settings:
    - Primary, specialty, inpatient

KQ 2: What are the comparative safety and effectiveness of pharmacologic and nonpharmacologic depression treatments in post-ACS patients?

- Population(s):
    - Adults who received a criterion-based diagnosis of depression and are within 3 months of an ACS event.
- Interventions (considered singly or in combination):
    - Medical Therapy
        - Antidepressant medications (SSRI, SNRI, etc.) limited to second generation medications which have been FDA-approved for treatment of major depressive disorder:
            - Bupropion
            - Citalopram
            - Desvenlafaxine
            - Duloxetine
            - Fluoxetine
            - Escitalopram
            - Levomilnacipran
            - Mirtazapine
            - Nefazodone
            - Paroxetine
            - Sertraline
            - Trazodone

        - Venlafaxine
        - Vilazodone
        - Vortioxetine
    - Atypical antipsychotics – limited to those that are FDA-approved for treatment of major depressive disorder:
        - Aripiprazole
        - Olanzapine
        - Quetiapine
    - Tricyclic antidepressants – limited to those that are FDA-approved for treatment of major depressive disorder:
        - Amitryptiline
        - Amoxapine
        - Desipramine
        - Doxepin
        - Imipramine
        - Nortryptiline
        - Protryptiline
        - Trimipramine
- Psychotherapy
    - Cognitive behavioral therapy, limited to: cognitive behavioral therapy (CBT), cognitive therapy, behavioral therapy, cognitive behavioral analysis system of psychotherapy, and behavioral activation
    - Problem solving therapy
    - Interpersonal psychotherapy
    - Short-term psychodynamic therapy
    - "Third wave" cognitive behavioral psychotherapies, limited to: acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), mindfulness, mindfulness-based cognitive therapy (MBCT), and functional analytic psychotherapy (FAP)
- Other Treatments
    - Structured aerobic exercise: Structured exercise is defined as regular physical activity done with the intention of improving or maintaining physical fitness or health, or performed as part of a class or with support from a health professional.

        - St John's Wort
        - Fish oil/ omega-3 fatty acids
        - S-Adenosylmethionine
        - Cardiac rehabilitation which typically includes supervised exercise training in conjunction with other secondary prevention interventions (e.g., psychosocial support, stress management, nutrition counseling, education on medication adherence).
        - Education/psychoeducation
        - Stress management: mindfulness meditation, progressive muscle relaxation, qigong meditation, spiritual medication, guided imagery-based approaches, paced respiration, Roll breathing, 4-7-8 breath technique
        - Psychosocial support
        - Transcranial magnetic stimulation
        - Electroconvulsive therapy (ECT)
    - Enhanced Care Delivery
        - Collaborative care in primary care or cardiology settings (Note that such care integrates psychiatric treatment into other settings. "Patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (e.g., psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (e.g., patient education or cognitive-behavioral therapy), scheduled followup visits, communication amongst the members of the treatment team, and measurement-based care."[29])
- Comparators:
    - Active comparator from listed interventions
- Outcomes:
    - Clinical outcomes
        - Total mortality
        - Depression-related outcomes
            - Response or remission of depressive symptoms using validated continuous or categorical measures
        - Cardiac-related outcomes
            - Cardiac mortality
            - Repeat ACS event (repeat MI or unstable angina)

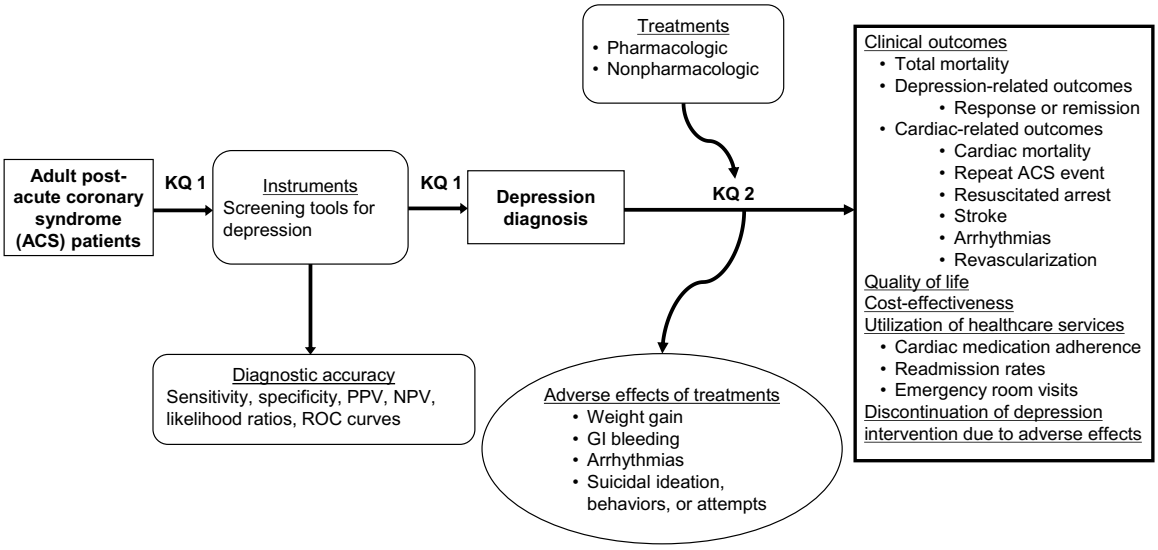
- Resuscitated arrest
- Stroke
- Arrhythmias
- Revascularization

- Quality of life (QOL)
- Cost-effectiveness
- Utilization of health care services
  - Cardiac medication adherence
  - Readmission rates due to cardiac and non-cardiac reasons
  - Emergency room visits (all visits, cardiac-related, and psychiatric-related)
- Discontinuation of depression intervention due to adverse effects
  - Adverse effects of treatment (excluding clinical outcomes listed above)Weight gain
  - Gastrointestinal (GI) bleeding
  - Arrhythmias
  - Suicidal ideation, behaviors, or attempts

- Timing:
  - At least 6 weeks of followup
  - Intervals of interest:
    - During hospitalization/at discharge
    - Within 30-days of hospitalization for an acute ACS event
    - Within 3 months of hospitalization for an acute ACS event
    - Beyond 3 months of hospitalization for an acute ACS event
- Settings:
  - Primary, specialty, inpatient

III. Analytic Framework

Figure 1. Analytic Framework



Abbreviations: ACS = acute coronary syndrome; GI = gastrointestinal; KQ = key question; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic

Figure 1 depicts the key questions within the context of the population, interventions, comparators, outcomes, timing, and settings (PICOTS) described in the previous section. In general, the figure illustrates how individuals who are post-acute coronary syndrome (ACS) may be screened and treated for depression, and how treatment is associated with a range of potential adverse effects and outcomes. Separate key questions address the accuracy of screening (KQ 1) and the effectiveness and risk of adverse events associated with pharmacologic and/or nonpharmacologic treatments (KQ 2).

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ)'s EPC Program in its Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[30] Throughout the project, we will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended by the EPCs for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

Criteria for Inclusion/Exclusion of Studies in the Review

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	KQ 1: Adults who have acute coronary syndrome (ACS) [which includes both unstable angina and myocardial infarction (MI)] and are within 3 months of an identifying ACS event. KQ 2: Adults who received a criterion-based diagnosis of depression and are within 3 months of an acute ACS event. Subgroups of interest: • Age (KQ 1, KQ 2) older adults (≥ 65 years) versus adults younger than 65 years of age • Race/ethnicity (KQ 1, KQ 2) • Sex (KQ 1, KQ 2) • In- vs outpatient (KQ 1)	Individuals younger than 18 years of age. Studies including mixed samples (e.g., both adults and patients under 18, those with ACS less than and more than 3 months prior) will be excluded unless data for the target population is reported separately. KQ 2: Depression diagnosis made by unstructured clinical diagnosis, chart diagnosis, or based on administrative codes or prescription for an antidepressant.

Interventions	KQ 1:
	• Screening tools for depression, limited to:
	  ○ Beck Depression Inventory (multiple versions)
	  ○ Center for Epidemiologic Studies-Depression (CES-D20 and CES-D10)
	  ○ Distress Questionnaire 5 (DQ5)
	  ○ Duke Anxiety and Depression Scale
	  ○ Geriatric Depression Scale (GDS-15) [2 versions, long and short]
	  ○ Hospital Anxiety and Depression Scale (HADS and HADS-D)
	  ○ Diagnostic Inventory for Depression (DID)
	  ○ Kessler Psychological Distress Scale (K10 and K6)
	  ○ Patient Health Questionnaire (PHQ-8/9 and 2)
	  ○ Primary care rapid evaluation of mental disorders (PRIME-MD, including Whooley questions)
	  ○ PROMIS® (Patient-Reported Outcomes Measurement Information System)
	  ○ Quick Inventory of Depressive Symptomatology (QIDS)
	  ○ Symptom Checklist 20 and Hopkins Symptom Checklist
	  ○ WHO-5 (World Health Organization-5)
	  ○ Zung Self-Rating Depression Scale (SDS)
	• Screening strategies that differ by setting (i.e, inpatient vs outpatient, general medicine vs cardiology) or timing (i.e., duration post-ACS event)
	
	KQ 2 (considered singly or in combination):
	• Medical Therapy
	  ○ Antidepressant medications (SSRI, SNRI, etc.) limited to second generation medications which have been FDA-approved for treatment
		KQ 2: Combination interventions that include an ineligible intervention

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	of major depressive disorder: ▪ Bupropion ▪ Citalopram ▪ Desvenlafaxine ▪ Duloxetine ▪ Fluoxetine ▪ Escitalopram ▪ Levomilnacipran ▪ Mirtazapine ▪ Nefazodone ▪ Paroxetine ▪ Sertraline ▪ Trazodone ▪ Venlafaxine ▪ Vilazodone ▪ Vortioxetine ○ Atypical antipsychotics – limited to those that are FDA-approved for treatment of major depressive disorder: ▪ Aripiprazole ▪ Olanzapine ▪ Quetiapine ○ Tricyclic antidepressants – limited to those that are FDA-approved for treatment of major depressive disorder: ▪ Amitryptiline ▪ Amoxapine ▪ Desipramine ▪ Doxepin ▪ Imipramine ▪ Nortryptiline ▪ Protryptiline ▪ Trimipramine • Psychotherapy ○ Cognitive behavioral therapy, limited to: cognitive behavioral therapy (CBT), cognitive therapy, behavioral therapy, cognitive behavioral analysis system of psychotherapy, and behavioral activation ○ Problem solving therapy ○ Interpersonal psychotherapy ○ Short-term psychodynamic therapy ○ "Third wave" cognitive behavioral psychotherapies, limited to: acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), mindfulness, mindfulness-based cognitive therapy (MBCT), and functional analytic psychotherapy (FAP) • Other Treatments ○ Structured aerobic exercise: Structured exercise is defined as regular physical activity done with the intention of improving or maintaining physical fitness or health, or	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	performed as part of a class or with support from a health professional. ○ St John's Wort ○ Fish oil/ omega-3 fatty acids ○ S-Adenosylmethionine ○ Cardiac rehabilitation which typically includes supervised exercise training in conjunction with other secondary prevention interventions (e.g., psychosocial support, stress management, nutrition counseling, education on medication adherence). ○ Education/psychoeducation ○ Stress management: mindfulness meditation, progressive muscle relaxation, qigong meditation, spiritual medication, guided imagery-based approaches, paced respiration, Roll breathing, 4-7-8 breath technique ○ Psychosocial support ○ Transcranial magnetic stimulation ○ Electroconvulsive therapy (ECT) • Enhanced Care Delivery ○ Collaborative care in primary care or cardiology settings (Note that such care integrates psychiatric treatment into other settings. "Patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (e.g., psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (e.g., patient education or cognitive-behavioral therapy), scheduled follow-up visits, communication amongst the members of the treatment team, and measurement-based care."[29])	
Comparators	KQ 1: Validated criterion standard (e.g., DSM or ICD criteria) administered by a trained interviewer KQ 2: Active comparator from listed interventions	KQ 2: Same treatment comparisons that vary by dose KQ 2: Combination comparators that include an ineligible intervention
Outcomes	KQ 1: • Diagnostic accuracy, as measured by: ○ Sensitivity ○ Specificity ○ Negative predictive value (NPV) ○ Positive predictive value (PPV) ○ Likelihood ratios ○ Receiver operating characteristic (ROC) curves KQ 2:	

PICOTS Element	Inclusion Criteria	Exclusion Criteria

	• Clinical outcomes
	  ○ Total mortality
	  ○ Depression-related outcomes
	  ▪ Response or remission of depressive symptoms using validated continuous or categorical measures
	  ○ Cardiac-related outcomes
	  ▪ Cardiac mortality
	  ▪ Repeat ACS event (repeat MI or unstable angina)
	  ▪ Resuscitated arrest
	  ▪ Stroke
	  ▪ Arrhythmias
	  ▪ Revascularization
	• Quality of life (QOL)
	• Cost-effectiveness
	• Utilization of health care services
	  ○ Cardiac medication adherence
	  ○ Readmission rates due to cardiac and non-cardiac reasons
	  ○ Emergency room visits: all visits, cardiac-related, and psychiatric-related
	• Discontinuation of depression intervention due to adverse effects
	• Adverse effects of treatment (excluding clinical outcomes listed above)
	  ○ Weight gain
	  ○ Gastrointestinal bleeding
	  ○ Arrhythmias
	  ○ Suicidal ideation, behaviors or attempts	

Timing	KQ 1: Within 3 months of an identifying ACS event KQ 2: At least 6 weeks of followup	
Settings	• Primary, specialty, and inpatient settings • Studies conducted in countries with similar cardiac care and similar concept of depressive disorders to that of the United States: North America, European Union and the UK, Australia, New Zealand	
Study design	• Original peer-reviewed data • KQ 1: Observational studies, sample size ≥50 subjects • KQ 2: Randomized controlled trials (RCTs), sample size ≥20 subjects	Editorials, nonsystematic reviews, letters, case series, case reports, abstract-only or poster publications, articles that have been retracted or withdrawn Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality,[31,32] we will

PICOTS Element	Inclusion Criteria	Exclusion Criteria
		exclude them from our review. For observational studies, we will require at least 50 subjects.
Publications	• English-language only • Published January 1, 2003, to present	Given the high volume of literature available in English-language publications, the focus of our review on applicability to populations in the United States, and the scope of our current KQs, non-English articles will be excluded[a]

[a]It is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

Abbreviations: ACS = acute coronary syndrome; ACT = acceptance and commitment therapy; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECT = electroconvulsive therapy; ICD = International Classification of Diseases; FAP = functional analytic psychotherapy; FDA = U.S. Food and Drug Administration; KQ = key question; MBCT = mindfulness-based cognitive therapy; MI = myocardial infarction; NPV = negative predictive value; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, Settings; PPV = positive predictive value; QOL = quality of life; ROC = receiver operating characteristic; RCTs = randomized controlled trials; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

To identify relevant published literature, we will search PubMed®, Embase®, PsycINFO®, CINAHL®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to articles published from January 1, 2003, to the present. These databases were selected based on: (1) internal expert opinion that they would identify most of the relevant literature on this topic and (2) the approaches of prior related systematic reviews. We believe that the evidence published from 2003 both represents the current standard of care for the population of interest in this review and allows this report to build on the previous systematic review[33] published in 2005 (which had an electronic search date through March 2004). Our proposed search strategy for PubMed is provided in Appendix B; this strategy will be adapted as appropriate for searching the other databases. Where possible, we will use existing validated search filters (such as the the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE). An experienced search librarian will guide all searches. While the draft report is under peer review, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our database, and additional relevant manuscripts will be retrieved. All citations will be imported into

an electronic bibliographical database (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

We will use several approaches to identifying relevant gray literature, including requests to drug and device manufacturers and other stakeholders for scientific information packets. These requests will be coordinated by AHRQ's Scientific Resource Center. Additional grey literature will be solicited through a notice posted in the Federal Register and on the AHRQ Effective Health Care website. As a mechanism to ascertain publication bias in recent studies, we will search ClinicalTrials.gov to identify completed but unpublished studies (we will also explore the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques). We will also search ClinicalTrials.gov for relevant articles from completed studies.

For citations retrieved from MEDLINE, Embase, PsycINFO, CINAHL, and the CDSR, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. Inclusion at the title and abstract screening level will be liberal; if a single reviewer believes an article may contain relevant information, the article will move to the next level for further screening. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Disagreements that cannot be resolved by the two reviewers will be resolved by a third expert member of the team. Articles meeting eligibility criteria (see Table 1) will be included for data abstraction. At random intervals during screening, quality checks by senior team members will occur to ensure that screening and abstraction is consistent with inclusion/exclusion criteria and abstraction guidelines. We will make screening decisions and abstract data based on the published literature and available online appendices. We will not contact study authors for additional data. All results will be tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. We will link studies to avoid duplication of patient cohorts.

We will design the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We will pay particular attention to describing the details of the screening approach (e.g., instrument version, administration mode),

details of the treatment (e.g., pharmacotherapy dosing, methods of behavioral interventions, co-interventions), patient characteristics (e.g., depressive disorder, age) that may be related to outcomes. In addition, we will describe comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes will be framed to help identify adverse events, including those from drug therapies and those resulting from misdiagnosis and labeling. Data necessary for assessing quality and applicability, as described in the Methods Guide,[30] will also be abstracted. Before they are used, abstraction form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency and reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles. Final abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) per EPC requirements.

Assessment of Methodological Risk of Bias of Individual Studies

We will assess methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias tool for randomized studies,[34,35] and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for observational studies.[36] We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ's Methods Guide.[30] Briefly, we will rate each RCT as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. Observational studies will be rated on each individual quality criteria and will not be given a summary rating. For each RCT, one investigator will assess methodological quality which will be reviewed by a second investigator; disagreements will be resolved by consensus or by a third investigator if agreement cannot be reached. For RCTs,[34] the overall study quality will be assessed as follows:

- Good (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.

- Fair. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- Poor (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The quality assessment will be outcome-specific such that a given study that analyzes its primary outcome well but did an incomplete analysis of a secondary outcome would be assigned a different quality grade for each of the two outcomes. We will apply this outcome-specific quality assessment to groups of outcomes that have lower risk of detection bias (e.g., mortality) and those at higher risk of detection bias (e.g,. depression symptoms). Studies of different designs will be evaluated within the context of their respective designs. Thus, RCT quality will be summarized as good, fair, or poor, and observational studies will be presented using QUADAS-2 graphics showing judgements for each quality item.

Data Synthesis

We will begin by summarizing key features of the included studies for each KQ. To the degree that data are available, we will abstract information on study design; patient characteristics; clinical settings; screening measure/interventions; and intermediate, final, and adverse event outcomes. We will order our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized.

We will review and highlight studies using a hierarchy-of-evidence approach. The best evidence available will be the focus of our synthesis for each key question. If high quality evidence is not available we will describe any lower quality evidence we were able to identify, but we will underscore the issues that make it lower quality and the uncertainties in our findings. We will assess and state whether the inclusion of lower quality studies would change any of our conclusions and perform sensitivity analyses excluding this evidence where appropriate.

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature (we will require 3 appropriate studies to consider meta-analysis of intervention studies and 3 to consider meta-analysis of observational diagnostic test studies), conceptual homogeneity of the studies, and completeness of the reporting of results. For meta-analyses summarizing the sensitivity and sensitivity of diagnostic rests, convergence problems of the bivariate random effects methodology may be encountered and we may need to revert to analysis sensitivity and specificity separately. When a meta-analysis is appropriate, we will use random-effects models to synthesize the available evidence quantitatively. For depressive symptoms and QOL, it is likely that studies will use different instruments to measure these constructs and results will be reported as a standardized mean difference (SMD); when appropriate the SMD will be transformed to natural units to aid interpretability. We will test for heterogeneity using graphical displays and test statistics (Q and I2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. For KQ1, we hypothesize that the methodological quality of individual studies, the spectrum of depressive disorders, and age of the sample will be associated with performance of the depression screeners. For KQ2, we hypothesize that the methodological quality of individual

studies, the characteristics of the comparator, and patients' underlying clinical presentation (e.g., depression severity and specific depressive diagnosis) will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses. We will perform quantitative and qualitative syntheses separately by study type and discuss their consistency qualitatively.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

With input from the TEP, we will select a specific set of comparisons and outcomes for strength of evidence grading. The aim will be to identify and grade those outcomes that are critical for decisionmaking. We will grade the strength of evidence for each selected outcome separately. The strength of evidence will be assessed using the approach described in AHRQ's Methods Guide. In brief, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias. For intervention trials, these domains affect the confidence in treatment effects. For diagnostic test studies, these factors affect the confidence in estimates of test accuracy and effects on patient management.[37] These domains will be considered qualitatively, and a summary rating of high, moderate, or low strength of evidence will be assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" will be assigned. This four-level rating scale consists of the following definitions:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.

- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Assessing Applicability

We will assess applicability across our key questions using the method described in AHRQ's Methods Guide.[30] In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, depression severity, psychiatric and medical comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We will use a checklist to guide the assessment of applicability. We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

V. References

1. World Health Organization. Global status report on noncommunicable diseases 2014. Available at: http://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed March 1, 2016.
2. Centers for Disease Control and Prevention (CDC). Deaths: Leading Causes for 2013. NVSR Volume 65, Number 2. 95 pp. (PHS) 2016-1250. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_02.pdf. Accessed March 1, 2016.
3. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital Health Stat 10. 2014 Feb(260):1-161. PMID: 24819891.
4. Centers for Disease Control and Prevention (CDC). Heart Disease Facts, 2015. Available at: http://www.cdc.gov/heartdisease/facts.htm. Accessed February 16, 2016.
5. Williams RB. Cardiology Patient Page. Depression after heart attack: why should I be concerned about depression after a heart attack? Circulation. 2011 Jun 28;123(25):e639-40. doi: 10.1161/circulationaha.110.017285. PMID: 21709066.
6. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593-602. doi: 10.1001/archpsyc.62.6.593. PMID: 15939837.
7. Guck TP, Kavan MG, Elsasser GN, et al. Assessment and treatment of depression following myocardial infarction. Am Fam Physician. 2001 Aug 15;64(4):641-8. PMID: 11529263.

8. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006 Jan;21(1):30-8. doi: 10.1111/j.1525-1497.2005.00269.x. PMID: 16423120.

9. Rapaport MH, Judd LL, Schettler PJ, et al. A descriptive analysis of minor depression. Am J Psychiatry. 2002 Apr;159(4):637-43. doi: 10.1176/appi.ajp.159.4.637. PMID: 11925303.

10. Williams JW, Jr., Kerber CA, Mulrow CD, et al. Depressive disorders in primary care: prevalence, functional disability, and identification. J Gen Intern Med. 1995 Jan;10(1):7-12. PMID: 7699487.

11. Jackson JL, Passamonti M, Kroenke K. Outcome and impact of mental disorders in primary care at 5 years. Psychosom Med. 2007 Apr;69(3):270-6. doi: 10.1097/PSY.0b013e3180314b59. PMID: 17401055.

12. Pincus HA, Davis WW, McQueen LE. 'Subthreshold' mental disorders. A review and synthesis of studies on minor depression and other 'brand names'. Br J Psychiatry. 1999 Apr;174:288-96. PMID: 10533546.

13. Karg RS, Bose J, Batts KR, et al. Past Year Mental Disorders among Adults in the United States: Results from the 2008–2012 Mental Health Surveillance Study. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality Data Review. http://www.samhsa.gov/data/sites/default/files/NSDUH-DR-N2MentalDis-2014-1/Web/NSDUH-DR-N2MentalDis-2014.pdf (Accessed June 20, 2016). October 2014.

14. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013 Nov;10(11):e1001547. doi: 10.1371/journal.pmed.1001547. PMID: 24223526.

15. Gartlehner G, Gaynes BN, Amick HR, et al. Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder. Comparative Effectiveness Review No. 161. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 15(16)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 26764438.

16. Siu AL, U.S. Preventive Services Task Force, Bibbins-Domingo K, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Jan 26;315(4):380-7. doi: 10.1001/jama.2015.18392. PMID: 26813211.

17. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence: Guidance. Depression in Adults with a Chronic Physical Health Problem: Treatment and Management. Leicester (UK): The British Psychological Society & The Royal College of Psychiatrists.; 2010.

18. Joffres M, Jaramillo A, Dickinson J, et al. Recommendations on screening for depression in adults. CMAJ. 2013 Jun 11;185(9):775-82. doi: 10.1503/cmaj.130403. PMID: 23670157.

19. . AAFP guideline for the detection and management of post-myocardial infarction depression. Ann Fam Med. 2009 Jan-Feb;7(1):71-9. doi: 10.1370/afm.918. PMID: 19139452.

20. Lichtman JH, Bigger JT, Jr., Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008 Oct 21;118(17):1768-75. doi: 10.1161/circulationaha.108.190769. PMID: 18824640.

21. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014 Jun 1;35(21):1365-72. doi: 10.1093/eurheartj/eht462. PMID: 24282187.

22. Moore RC, Chattillion EA, Ceglowski J, et al. A randomized clinical trial of Behavioral Activation (BA) therapy for improving psychological and physical health in dementia caregivers: results of the Pleasant Events Program (PEP). Behav Res Ther. 2013 Oct;51(10):623-32. doi: 10.1016/j.brat.2013.07.005. PMID: 23916631.

23. Craft LL, Perna FM. The Benefits of Exercise for the Clinically Depressed. Prim Care Companion J Clin Psychiatry. 2004;6(3):104-11. PMID: 15361924.

24. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med. 2004 May 15;116(10):682-92. doi: 10.1016/j.amjmed.2004.01.009. PMID: 15121495.

25. Williams JW, Jr., Noel PH, Cordes JA, et al. Is this patient clinically depressed? JAMA. 2002 Mar 6;287(9):1160-70. PMID: 11879114.

26. Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. CMAJ. 2008 Apr 8;178(8):997-1003. doi: 10.1503/cmaj.070281. PMID: 18390942.

27. Zimmerman M, Sheeran T, Young D. The Diagnostic Inventory for Depression: a self-report scale to diagnose DSM-IV major depressive disorder. J Clin Psychol. 2004 Jan;60(1):87-110. doi: 10.1002/jclp.10207. PMID: 14692011.

28. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003 Sep 1;54(5):573-83. PMID: 12946886.

29. Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev. 2012;10:Cd006525. doi: 10.1002/14651858.CD006525.pub2. PMID: 23076925.

30. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed July 16, 2015.

31. Dechartres A, Trinquart L, Boutron I, et al. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ. 2013;346:f2304. doi: 10.1136/bmj.f2304. PMID: 23616031.

32. Dechartres A, Altman DG, Trinquart L, et al. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. JAMA. 2014 Aug 13;312(6):623-30. doi: 10.1001/jama.2014.8166. PMID: 25117131.

33. Bush DE, Ziegelstein RC, Patel UV, et al. Post-myocardial infarction depression. Evid Rep Technol Assess (Summ). 2005 May(123):[Archived]. PMID: 15989376.

34. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.

35. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org: The Cochrane Collaboration; 2011.

36. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 2007046.

37. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008 May 17;336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE. PMID: 18483053.

VI. Definition of Terms

ACS	Acute Coronary Syndrome
ACT	Acceptance and commitment therapy
AE	Adverse effect
AHRQ	Agency for Healthcare Research and Quality
CBT	Cognitive behavioral therapy
CDSR	Cochrane Database of Systematic Reviews
DBT	Dialectical behavior therapy

DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
EPC	Evidence-based Practice Center
FAP	Functional analytic psychotherapy
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
ICD	International Classification of Diseases
KQ	Key question
MBCT	Mindfulness-based cognitive therapy
MDD	Major depressive disorder
MI	Myocardial infarction
NPV	Negative predictive value
NSTEMI	Non-ST-segment elevation myocardial infarction
PICOTS	Population, interventions, comparators, outcomes, timing, settings
PPV	Positive predictive value
QOL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SMD	Standardized mean difference
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitors
SRDR	Systematic Review Data Repository
STEMI	ST-segment elevation myocardial infarction
TEP	Technical Expert Panel
TOO	Task Order Officer
UA	Unstable angina
USPSTF	United States Preventive Services Task Force

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290201500004I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A: FDA Status and Warnings for Drugs Included in this Review

Appendix Table A1. Second-generation antidepressant medications that are FDA-approved for treatment of major depressive disorder[1]

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
Warnings: All antidepressants have a black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age. There is also a risk of withdrawal symptoms if discontinued abruptly. Other risks of SSRI/SNRIs: bleeding, fracture, narrow angle glaucoma, serotonin syndrome, sexual dysfunction, syndrome of inappropriate antidiuretic hormone secretion (SIADH). Many antidepressants have cautions for use in patients with angle-closure glaucoma, bipolar disorder, pregnancy in 3rd trimester, seizure disorders		
Atypical antidepressants		
Bupropion	Yes	Contraindicated in seizure disorders or eating disorders
Mirtazapine	Yes	–
Nefazodone	Yes	Hepatic failure
Trazodone	Yes	–
Vilazodone[2]	Yes	–
Vortioxetine[3]	Yes	–
SSRIs		
Citalopram	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF; Reduce dose if age >60
Fluoxetine	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF
Escitalopram	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF
Paroxetine	Yes	–
Sertraline	Yes	–
SNRIs		
Desvenlafaxine	Yes	Cardiovascular disesease

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
Duloxetine	Yes	Hypertension
Levomilnacipran[4]	Yes	Cerebrovascular disease, Cardiovascular disease, Hypertension, ≥ Stage 3 CKD
Venlafaxine	Yes	Heart failure, recent MI

Abbreviations: MI = myocardial infarction; CHF = congestive heart failure; CKD = chronic kidney disease; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin–norepinephrine reuptake inhibitors

Appendix Table A2. Atypical antipsychotics that are FDA-approved for treatment of major depressive disorder[1]

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
Warnings: Black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age (Aripiprazole and Quetiapine). Black box warning for increased risk of death in elderly patients with dementia-related psychosis. Other risks related to atypical antipsychotics: altered cardiac conduction (prolonged QTc), blood dyscrasia, increased stroke in dementia related psychosis, CNS depression, anticholinergic effect, dyslipidemia, hyperlipidemia, aspiration, extrapyramidal symptoms, neuroleptic malignant syndrome, orthostatic hypotension, pathologic gambling, impaired temperature regulation, weight gain and metabolic side effects.		
Aripiprazole[5]	Yes, as an adjunct with an antidepressant	FDA safety alert: uncontrollable urges to gamble, binge eat, shop or have sex. Other risks: akathisia, restlessness, sedation, headache, nausea and vomiting
Olanzapine[6]	For bipolar depression and treatment resistant depression, only in combination with fluoxetine	FDA safety alert: DRESS (drug reaction with eosinophilia and systemic symptoms) FDA black box: delirium/sedation syndrome with long acting injection (likely not relevant to use in depression) Other risks: akathisia, sedation, dizziness, headache, increased prolactin Risk of suicidal thoughts and behavior but

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
		does not have black box.
Quetiapine[7]	Yes, as an adjunct with an antidepressant	Other risks: sedation, hypertension, cataracts, hypothyroidism, headache, tachycardia, increased prolactin

Abbreviations: CNS = central nervous system; QTc = corrected QT interval

Appendix Table A3. Tricyclic antidepressants that are FDA-approved for treatment of major depressive disorder[1]

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
Warnings: All antidepressants have a black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age. Contraindicated for use with or within 14 days of concomitant monoamine oxidase inhibitor (MAOI) therapy. Tricyclic antidepressants are contraindicated during the acute recovery period following a myocardial infarction. There is also a risk of withdrawal symptoms if discontinued abruptly. Tricyclic antidepressants should be used with caution in patients with a history of cardiovascular disease due to the risk of conduction abnormalities. Other risks related to tricyclic antidepressants include altered cardiac conduction (prolonged QTc), orthostatic hypotension, anticholinergic effects (including but not limited to constipation, urinary retention and blurred vision) and CNS depression including sedation. Tricyclic antidepressants should be used with caution in individuals with bipolar disorder, the elderly and those with hepatic impairment or a history of seizures.		
Amitryptiline[8-9]	Yes	–
Amoxapine[10-11]	Yes	History of neuroleptic malignant syndrome, high environmental temperatures
Desipramine[12-13]	Yes	–
Doxepin	Yes	–
Imipramine[14-15]	Yes	–
Nortryptiline[16-17]	Yes	–

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
Protryptiline[18-19]	Yes	–
Trimipramine	Yes	–

Abbreviations: CNS = central nervous system; MAOI = monoamine oxidase inhibitor; QTc = corrected QT interval

Notes to Appendix Tables A1, A2, and A3:

1. Depression: Medicines to Help You. FDA office of women's Health. http://www.fda.gov/downloads/ForConsumers/ByAudience/ForWomen/FreePublications/UCM182083.pdf

2. Vilazodone: Drug Information. http://www.uptodate.com/contents/vilazodone-drug-information?source=search_result&search=vilazodone&selectedTitle=1%7E13#F11595949

3. Vorioxetine: Drug Information. http://www.uptodate.com/contents/vortioxetine-drug-information?source=search_result&search=vortioxetine&selectedTitle=1%7E8

4. Levomilnacipran: Drug Information. http://www.uptodate.com/contents/levomilnacipran-drug-information?source=search_result&search=levomilnacipran&selectedTitle=1%7E6

5. Aripiprazole: Drug Information. http://www.uptodate.com/contents/aripiprazole-short-acting-oral-and-injectable-and-long-acting-injectable-abilify-maintena-drug-information?source=search_result&search=abilify&selectedTitle=1%7E62

6. Olanzapine: Drug Information. http://www.uptodate.com/contents/olanzapine-drug-information?source=search_result&search=zyprexa&selectedTitle=1%7E121

7. Quetiapine: Drug Information. http://www.uptodate.com/contents/quetiapine-drug-information?source=search_result&search=quetiapine&selectedTitle=1%7E105

8. Amitriptyline: Product Information: amitriptyline hcl oral tablets, amitriptyline hcl oral tablets. Vintage Pharmaceuticals,LLC, Huntsville, AL, 2006.

9. Amitriptyline: Drug Information. http://www.uptodate.com/contents/amitriptyline-drug-information?source=search_result&search=Amitriptyline&selectedTitle=1~139

10. Amoxapine: Product Information: amoxapine oral tablets, amoxapine oral tablets. Watson Pharma, Inc. (per DailyMed), Parsippany, NJ, 2014.

12. Amoxapine: Drug Information. http://www.uptodate.com/contents/amoxapine-drug-information?source=search_result&search=amoxapine&selectedTitle=1~8

12. Desipramine: Product Information: NORPRAMIN(R) oral tablets, desipramine HCl oral tablets. Sanofi-Aventis U.S. LLC (per FDA), Bridgewater, NJ, 2014

13. Desipramine: Drug Information. http://www.uptodate.com/contents/desipramine-drug-information?source=search_result&search=Desipramine&selectedTitle=1~74

14. Imipramine: Product Information: Tofranil-PM(TM) oral capsules, imipramine pamoate oral capsules. Mallinckrodt Inc. (per FDA), Hazelwood, MO, 2014.

15. Imipramine: Drug Information. http://www.uptodate.com/contents/imipramine-drug-information?source=search_result&search=Imipramine&selectedTitle=1~76

16. Nortriptyline: Product Information: Pamelor(TM) oral solution, nortriptyline HCl oral solution. Mallinckrodt Inc. (per FDA), Hazelwood, MO, 2014.

17. Nortriptyline: Drug Information. http://www.uptodate.com/contents/nortriptyline-drug-information?source=search_result&search=Nortriptyline&selectedTitle=1~92

18. Protriptyline: Product Information: VIVACTIL(R) film-coated tablets, protriptyline HCl film-coated tablets. Teva Pharmaceuticals USA, Inc. (per FDA), Horsham, PA, 2014.

19. Protriptyline: Drug Information. http://www.uptodate.com/contents/protriptyline-drug-information?source=search_result&search=Protriptyline&selectedTitle=1~19

Appendix B: PubMed Search Strategies

Appendix Table B1. PubMed search strategy for KQ 1

Set	Terms
#1	"Myocardial Infarction"[Mesh] OR "myocardial infarction"[tiab] OR "myocardial infarct"[tiab] OR "myocardial infarctions"[tiab] OR "heart infarction"[tiab] OR "heart infarct"[tiab] OR "heart infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab]
#2	"Acute Coronary Syndrome"[Mesh] OR "acute coronary syndrome"[tiab]
#3	"Depression"[Mesh] OR "Mental Disorders"[Mesh] OR depression[tiab] OR depressive[tiab] OR "mood disorder"[tiab] OR "mood disorders"[tiab] OR "psychiatric disorder"[tiab] OR "psychiatric disorders"[tiab]
#4	"Depression/diagnosis"[Mesh] OR mass screening[mesh] OR questionnaires[mesh] OR Interviews as Topic[Mesh] OR Psychometrics[Mesh] OR Psychiatric Status Rating Scales[Mesh] OR questionnaire[tiab] OR questionnaires[tiab] OR screening[tiab] OR screen[tiab] OR scale[tiab] OR instrument[tiab] OR instruments[tiab] OR inventory[tiab] OR BDI[tiab] OR "beck depression inventory"[tiab] OR CES-D20[tiab] OR CES-D10[tiab] OR “Center for Epidemiologic Studies Depression Scale”[tiab] OR HADS[tiab] OR "HADS-D"[tiab] OR “Hospital Anxiety and Depression Scale”[tiab] OR PHQ-9[tiab] OR “Patient Health Questionnaire-9”[tiab] OR PHQ-8[tiab] OR “Patient Health Questionnaire-8”[tiab] OR “Zung SDS”[tiab] OR “Zung Self-Rating Depression Scale”[tiab] OR “Zung Self Assessment Depression Scale”[tiab] OR "symptom checklist 20"[tiab] OR "Hopkins symptom checklist"[tiab] OR "Kessler psychological distress scale"[tiab] OR "distress questionnaire 5"[tiab] OR "geriatric depression scale"[tiab] OR "gds-15"[tiab] OR "primary care rapid evaluation of mental disorders"[tiab] OR "prime-md"[tiab] OR "duke anxiety and depression scale"[tiab] OR "inventory to diagnose depression"[tiab] OR "IDS"[tiab] OR "world health organization 5"[tiab] OR "who-5"[tiab] OR "Quick Inventory of Depressive Symptomatology"[tiab] OR promis[tiab] OR "patient reported outcomes measurement information system"[tiab]
#5	(systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "Cross-Sectional Studies"[Mesh] OR "cross sectional"[tiab]"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal”[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh]) AND English[la] AND ("2003/01/01"[Date - Publication] : "3000"[Date - Publication])
#6	(#1 OR #2) AND #3 AND #4 AND #5

Appendix Table B2. PubMed search strategy for KQ 2

Set	Terms
#1	"Myocardial Infarction"[Mesh] OR "myocardial infarction"[tiab] OR "myocardial infarct"[tiab] OR "myocardial infarctions"[tiab] OR "heart infarction"[tiab] OR "heart infarct"[tiab] OR "heart infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab]
#2	"Acute Coronary Syndrome"[Mesh] OR "acute coronary syndrome"[tiab]
#3	"Depression"[Mesh] OR "Mental Disorders"[Mesh] OR depression[tiab] OR depressive[tiab] OR "mood disorder"[tiab] OR "mood disorders"[tiab] OR "psychiatric disorder"[tiab] OR "psychiatric disorders"[tiab]
#4	"Depression/therapy"[Mesh] OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "Antidepressive Agents, Second-Generation" [Pharmacological Action] OR "Aripiprazole"[Mesh] OR "olanzapine"[Supplementary Concept] OR "Quetiapine Fumarate"[Mesh] OR "Fish Oils"[Mesh] OR "Psychotherapy"[Mesh] OR "Exercise"[Mesh]

Set	Terms
	OR "Physical Therapy Modalities"[Mesh] OR "Cardiovascular Diseases/rehabilitation"[Majr] OR "Hypericum"[Mesh] OR "Health Education"[Mesh] OR "Stress, Psychological"[Mesh] OR "Adaptation, Psychological"[Mesh] OR "Electroconvulsive Therapy"[Mesh] OR "continuity of patient care"[mesh] OR "Delivery of Health Care, Integrated"[Mesh] OR "Patient Care Team"[Mesh] OR "Patient Care Planning"[Mesh] OR "Disease Management"[Mesh] OR "Comprehensive Health Care"[Mesh:NoExp] OR "Patient Care Management"[Mesh:NoExp] OR "Transcranial Magnetic Stimulation"[Mesh] OR "S-Adenosylmethionine"[Mesh] OR amitriptyline[tiab] OR bupropion[tiab] OR citalopram[tiab] OR Desipramine[tiab] OR desvenlafaxine[tiab] OR Doxepin[tiab] OR duloxetine[tiab] OR fluoxetine[tiab] OR escitalopram[tiab] OR Imipramine[tiab] OR levomilnacipran[tiab] OR mirtazapine[tiab] OR nefazodone[tiab] OR paroxetine[tiab] OR Protriptyline[tiab] OR sertraline[tiab] OR trazodone[tiab] OR Trimipramine[tiab] OR venlafaxine[tiab] OR vilazodone[tiab] OR vortioxetine[tiab] OR aripiprazole[tiab] OR nortriptyline[tiab] OR olanzapine[tiab] OR quetiapine[tiab] OR Amoxapine[tiab] OR antidepressants[tiab] OR antidepressant[tiab] OR "fish oil"[tiab] OR "fish oils"[tiab] OR "fatty acid"[tiab] OR "fatty acids"[tiab] OR "omega 3"[tiab] OR "psychotherapy"[tiab] OR "behavior therapy"[tiab] OR "behavioral therapy"[tiab] OR "behaviour therapy"[tiab] OR "behavioural therapy"[tiab] OR "cognitive therapy"[tiab] OR "problem solving therapy"[tiab] OR "psychodynamic therapy"[tiab] OR mindfulness[tiab] OR "acceptance and commitment therapy"[tiab] OR "behavioral activation"[tiab] OR "behavioural activation"[tiab] OR "behavioral action"[tiab] OR "behavioural action"[tiab] OR exercise[tiab] OR psychosocial[tiab] OR "cardiac rehabilitation"[tiab] OR "physical therapy"[tiab] OR hypericum[tiab] OR "st john's wort"[tiab] OR "saint john's wort"[tiab] OR education[tiab] OR psychoeducation[tiab] OR stress[tiab] OR "collaborative care"[tiab] OR "care management"[tiab] OR "case management"[tiab] OR "disease management"[tiab] OR "enhanced care"[tiab] OR "managed care"[tiab] OR multidisciplinary[tiab] OR interprofessional[tiab] OR "team care"[tiab] OR "team consultation"[tiab] OR "team treatment"[tiab] OR "shared care"[tiab] OR "Transcranial Magnetic Stimulation"[tiab] OR "S-Adenosylmethionine"[tiab]
#5	(systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) AND English[la] AND ("2003/01/01"[Date - Publication] : "3000"[Date - Publication])
#6	(#1 OR #2) AND #3 AND #4 AND #5